IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE PROCTER & GAMBLE COMPANY, Plaintiff, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 04-940-JJF

PLAINTIFF THE PROCTER & GAMBLE COMPANY'S
ANSWERING POST-TRIAL REPLY BRIEF

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I. Teva's Post-Trial Brief Changes Nothing: The '122 Patent is Valid.

Unable to prove their case at trial, and having failed to carry their heavy and unshifting burden of proof, Teva's post-trial brief ("Teva Br.") adopts a novel strategy: pretending that the trial in this case never took place. Refusing to address the facts in the record and the controlling legal standards, Teva instead fills its brief with inaccurate and unsupported assertions intended to misdirect this Court. The law and the facts, however, are clear. Teva failed to prove by clear and convincing evidence that the '122 patent is invalid for obviousness under either 35 U.S.C. § 103 or under the judicially-created doctrine of obviousness-type double patenting. As discussed below and in P&G's opening post-trial brief ("P&G Br."), Teva's reliance on irrelevant evidence, inapposite legal standards, and mistaken characterizations changes nothing. Instead, Teva's brief confirms what the law and the evidence demonstrated before, during, and after trial – that the '122 patent is valid.

II. Teva's Post-Trial Brief Misapprehends and Misstates the Facts and Law.

At trial, Teva failed to meet its burden of proving invalidity by clear and convincing evidence. As a result, Teva's brief resorts to repeated misstatements and reliance on irrelevant or, worse, inaccurate facts and law. Teva's erroneous legal and factual assertions are myriad, the most egregious of which include:

- Refusing to acknowledge, ***or even mention***, anywhere in its fifty-three page brief that it is ***Teva's*** heavy and unshifting burden to prove invalidity of the '122 patent by clear and convincing evidence. *See Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006).

- Failing to apply the proper legal analysis for obviousness-type double patenting, which requires that the reference patent claim *as a whole* must be compared to the claim at issue. *See General Foods Corp. v. Studiengesellschaft Kohle*, 972 F.2d 1272, 1274-1275 (Fed. Cir. 1992). Instead, Teva uses ellipses to omit the heart of claim 15 of the '406 patent – a dosing regimen – and selectively and improperly chooses a *single* compound out of numerous compounds listed in claim 15 to compare against the asserted claims of the '122 patent. (*See* Teva Br. at 17-19, 24-45; DTX 309; DTX 311; DTX 312.)

- Conflating the analytically distinct concepts of anticipation-type double patenting and obviousness-type double patenting to incorrectly assert that objective indicia of non-obviousness are not to be considered in an obviousness-type double patenting analysis. *See Eli Lilly & Co. v. Zenith Goldline Pharms. USA, Inc.*, 364 F. Supp.2d 820, 911 (S.D. Ind. 2005).

- Incorrectly suggesting that the question of whether there is a "reasonable expectation of success" is limited to an inquiry as to whether there is any "activity useful in treating diseases involving calcium and phosphate metabolism." (Teva Br. at 30.) This standard ignores toxicity altogether, as well as relative potency. The benefit of risedronate and what Dr. Benedict hoped to achieve was a *more* potent bisphosphonate that was safe and did not inhibit bone mineralization. (*See* P&G Br. at 23.)

- Misstating the law with respect to unexpected results by suggesting that a "difference in kind" rather than a "difference in degree" must be proven. (Teva Br. at 32-33.) The Federal Circuit, however, has stated, "[o]ur cases make clear that there is no hard-and-fast rule for determining whether evidence of unexpected results is sufficient." *Kao*, 441 F.3d at 970.

- Wrongly stating that an inventor's unwitnessed lab notebook is insufficient to corroborate conception and that Dr. Benedict's unwitnessed notebooks "can not [sic] as a matter of law be relied upon to corroborate Dr. Benedict's oral testimony of conception" (Teva Br. at 50-51.) In fact, courts apply a "rule of reason" analysis to determine whether an inventor's prior conception testimony is corroborated, evaluating all pertinent evidence "so that a sound determination of the credibility of the inventor's story may be reached." *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993).

- Making unfounded insinuations about the authenticity of P&G's documentary evidence, but offering ***no evidence*** to rebut P&G's evidence of conception or reduction to practice of the patented invention.

- Relying on unsupported and legally irrelevant speculation about what P&G "could have" done and what "would probably have" occurred during an interference proceeding that was mentioned by Teva *one time* during trial and then only during Teva's opening statement. (Teva Br. at 11-12; Tr. Cite 8:2-5.)

- Suggesting without any basis whatsoever that P&G engaged in inequitable conduct, despite *never* raising it as an affirmative defense before or during trial. (Teva Br. at 13.) Such "unsupported accusations of inequitable conduct are a negative contribution to the administration of justice and should be condemned." *Total Containment, Inc. v. Environ Products, Inc.*, 921 F. Supp. 1355, 1406 (E.D. Pa. 1995), *aff'd*, 106 F.3d 427 (Fed. Cir. 1997) (unpublished).

- Misrepresenting that P&G stipulated that "the '543 application does not support any of the asserted claims of the '122 patent." (Teva Br. at 3, n.1). In actuality,

> P&G stipulated that "for purposes of [this] litigation only, it will not pursue at trial the argument that claims 4, 16 and 23 of the '122 patent are described in the '543 application." (D.I. 86.) Moreover, the parties agreed that the "stipulation is ***not evidence of the invalidity of any claim of the '122 patent*** or any other patent belonging to P&G." *Id.* (emphasis added).

Taken as a whole, these and other erroneous assertions demonstrate that Teva cannot marshal the requisite proof under the appropriate legal standards necessary to render the '122 patent obvious either under 35 U.S.C. § 103 or under the doctrine of obviousness-type double patenting. As such, the Court should find the '122 patent infringed and valid, and enter judgment in favor of P&G.

III. Teva Refuses to Acknowledge Its Burden of Proof of Clear and Convincing Evidence.

The most glaring omission in Teva's post-trial brief is its failure to address—***or even acknowledge***—its burden of proof. As an admitted infringer of the '122 patent, (*see* D.I. 63), Teva must demonstrate ***by clear and convincing*** evidence that the patent-in-suit is invalid to prevail in this case. *See, e.g., Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006) ("infringer seeking to invalidate a patent on obviousness grounds must establish its obviousness by facts supported by clear and convincing evidence"); *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1353 (Fed. Cir. 2003); *Forest Labs. v. Ivax Pharm., Inc.*, 438 F. Supp.2d 479, 485 (D. Del. 2006) (accused infringer failed to rebut presumption of validity by "clear and convincing evidence"). This heavy burden applies to both Teva's Section 103 obviousness and double patenting attacks on the validity of the '122 patent, and is "static, never-changing." *Magnivision, Inc. v. Bonneau Co.*, 115 F.3d 956, 958 (Fed. Cir. 1997) ("[T]he burden of proof does not change during the trial"); *Innovative Scuba Concepts, Inc. v. Feder Indus., Inc.*, 26 F.3d 1112, 1115 (Fed. Cir. 1994) ("[T]he ultimate burden of proving invalidity remains with the challenger throughout the litigation"); *Symbol Techs., Inc. v.*

Opticon, Inc., 935 F.2d 1569, 1580 (Fed. Cir. 1991) (defendant "required to prove double patenting by clear and convincing evidence, a heavy and unshifting burden"); *RCA Corp. v. Applied Digital Data Sys., Inc.*, 730 F.2d 1440, 1444 (Fed. Cir. 1984) (invalidity requires clear and convincing proof, and burden remains at all times with patent challenger).

Despite this well-settled law, Teva's brief is devoid of even a single mention of the "clear and convincing" evidence standard that it must meet. In fact, instead of acknowledging its heavy burden of proof, Teva repeatedly suggests that the proper obviousness inquiry is only whether risedronate is *prima facie* obvious in light of 2-pyr EHDP, and whether P&G, to whom Teva suggests the burden of proof shifts, can demonstrate that risedronate possesses unexpected properties to rebut that *prima facie* showing. (*See* Teva Br. at 25, 32-33, 45.) Teva's position is incorrect.

Teva fails to recognize that the *prima facie* obviousness inquiry and subsequent shifting burden of proof apply in *ex parte* cases before the PTO.[1] *See, e.g., In re Harris*, 409 F.3d 1339, 1343 (Fed. Cir. 2005) ("When the PTO shows prima facie obviousness, the burden then shifts to the applicant to rebut."). In patent infringement cases such as this one, where the patent-in-suit is presumed valid, "[t]he presumption does not dissolve and the burden of proof does not change during the trial; rather, the evidence presented by the challenger must be of such quality and weight as to establish invalidity [by clear and convincing evidence] despite the presumption." *Magnivision*, 115 F.3d at 958; *see also Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579

[1] In suggesting that a shifting of the burden of proof is appropriate, Teva primarily relies on *ex parte* decisions involving proceedings before the PTO, rather than *inter partes* cases. The rules and burdens of proof that apply in such *ex parte* proceedings are inapplicable to a district court patent infringement action such as this one. *Compare In re Harris*, 409 F.3d at 1343 (burden shifts to patent applicant after PTO demonstrates *prima facie* obviousness) with *Magnivision*, 115 F.3d at 958 (due to presumption of validity, burden of clear and convincing evidence remains on alleged infringer throughout trial).

(Fed. Cir. 1983) ("35 U.S.C. § 282 permanently places the burden of proving facts necessary to a conclusion of invalidity on the party asserting such invalidity."); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed. Cir. 1983) ("the burden of persuasion on the merits remains with that [patent challenger] until final decision").[2] As set forth below, Teva failed to meet this challenge at trial. (*See* P&G Br. at 11-34).

IV. Teva Failed to Meet its Burden of Proving the '122 Patent is Invalid by Clear and Convincing Evidence

Despite its heavy burden of proof, Teva presented only one witness—Dr. Lenz—to offer affirmative evidence regarding the validity of the '122 patent. However, as demonstrated at trial and described in P&G's opening brief, Dr. Lenz was not qualified to offer an opinion on obviousness in this case. (*See* P&G Br. at 11-20.) Moreover, even if he were qualified, his opinions do not constitute clear and convincing evidence of obviousness, given the overwhelming evidence of nonobviousness presented at trial by P&G. (*See* P&G Br. at 35-44.)

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[2] While the Federal Circuit does discuss *prima facie* obviousness in the context of patent infringement cases, it nevertheless has made clear that a *prima facie* case does not carry or shift the burden of proof. In *Innovative Scuba Concepts, Inc. v. Feder Indust., Inc.*, 26 F.3d 1112 (Fed. Cir. 1994), the court explained:

> Under 35 U.S.C. § 282, a patent is presumed valid and one challenging its validity bears the burden of proving invalidity by clear and convincing evidence. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). ***While a patentee may have the burden of going forward with rebuttal evidence once a challenger has presented a prima facie case of invalidity, the presumption of validity remains intact and the ultimate burden of proving invalidity remains with the challenger throughout the litigation.*** *See id.* at 1376. The role of the trial court is to determine whether the challenger has carried its burden, and it requires full consideration of all relevant evidence, including that presented in rebuttal. *See Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d at 1561, 1570 (Fed. Cir. 1987).
>
> *Id.* at 1115. (emphasis added).

A. Dr. Lenz Is Not Qualified to Opine on the Knowledge and Understanding of One of Ordinary Skill in the Art in the Mid-1980s

Although Teva suggests that its sole technical expert is qualified to opine on the obviousness of the '122 patent because he worked in drug discovery, (Teva Br. at 15), the evidence demonstrates otherwise.[3] Dr. Lenz is not qualified to offer an opinion on obviousness in this particular case because he lacks the requisite knowledge, skill, experience, training and education in or ganophosphorus compounds, and in particular bisphosphonates, necessary to render a reliable and admissible opinion. *See, e.g., Lauria v. Nat'l R.R. Passenger Corp.*, 145 F.3d 593, 597 (3d Cir. 1998) (proffered witness must possess the necessary knowledge, skill, training or education to assist the trier of fact).

Dr. Lenz's lack of requisite qualifications was exposed during trial.[4] In particular, on cross-examination Dr. Lenz admitted that he:

- Never worked with bisphosphonates during his entire professional career (PFF ¶ 97; Tr. at 170 (Lenz Cross));
- Has no formal education or training in bisphosphonates, osteoporosis, or the treatment of bone disease (PFF ¶ 95; Tr. at 168:1-13 (Lenz Cross));
- Never made a bisphosphonate or supervised any research concerning bisphosphonates (PFF ¶ 97; Tr. at 153; 157 (Lenz Cross));
- Never supervised any research directed to developing compounds for the treatment of osteoporosis, or any metabolic bone disease (PFF ¶ 98; Tr. at 157-58 (Lenz Cross));

[3] In its brief, Teva incredibly suggests that Dr. Lenz is *more* qualified than P&G's expert, Dr. Charles McKenna, who is one of the foremost experts on bisphosphonates. (Teva Br. at 16.) Dr. McKenna's qualifications are unimpeachable. (*See* P&G Br. at 13-14.) For Teva to suggest otherwise—particularly after seeing both witnesses testify at trial—is a further example of Teva's efforts to ignore the record evidence in this case.

[4] During trial, Dr. Lenz's lack of qualifications was exemplified by his need to resort to reading scripted testimony. (Tr. at 276:10-11 (Lenz. Dir.)). *See also* Tr. at 276:20-21 (Mr. Lee's statement, after examining the "notes" Dr. Lenz was reading from during his redirect testimony: "These are typed up statements of what he wants to say.") (Lenz Re-Dir.)).

- Never published on either bisphosphonates or osteoporosis (PFF ¶¶ 99-100; Tr. at 158:2 – 162:3 (Lenz Cross));
- Never made a presentation on organophosphorus compounds, bisphosphonates, or osteoporosis (PFF ¶ 102; Tr. at 165:10-166:1 (Lenz Cross));
- Holds no patents concerning bisphosphonates, osteoporosis, or the treatment of diseases related to abnormal calcium or phosphate metabolism (PFF ¶ 99-101; Tr. at 158; 161-62; 165-66 (Lenz Cross));
- Did not work in bisphosphonates or phosphorus chemistry in the mid-1980s (PFF ¶ 220; Tr. at 203:7-9 (Lenz Cross));
- Had never even heard of (let alone conducted or supervised) either the Schenk or TPTX assays before being hired by Teva (PFF ¶¶ 104-106; Tr. at 176-77, 180-81, 203:7-9 (Lenz Cross));
- Had no specific knowledge of the mechanisms of action of bisphosphonates before being hired by Teva (PFF ¶ 103; Tr. at 154 (Lenz Cross)); and
- Had absolutely no hands-on experience with any kind of bisphosphonate, including risedronate, before beginning his work in this litigation (PFF ¶ 97; Tr. at 153-54; 182 (Lenz Cross)).

Even apart from his lack of necessary qualifications, Dr. Lenz's opinions are inadmissible because they are premised on a legally improper hindsight analysis. (*See* P&G Br. at 18-20.) *See also, e.g.*, *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1290 (Fed. Cir. 2006) ("anti-hindsight jurisprudence is a test that rests on the unremarkable premise that legal determinations of obviousness, as with such determinations generally, should be based on evidence rather than on mere speculation or conjecture"). For example, at trial, Dr. Lenz admitted that to familiarize himself with bisphosphonates after being hired by Teva, he reviewed the drug profiles of various bisphosphonates, including risedronate, etidronate and alendronate, in the ***current version*** of the Physician's Desk Reference. (PFF ¶ 108; Tr. at 182-83, 193 (Lenz Cross)). However, Dr. Lenz did not review drug profiles from the relevant time period—the mid-1980s—and therefore failed to "cast[] [his] mind back to the time of invention." *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000); (PFF ¶ 109; Tr. at 194 (Lenz Cross)). As a result, it is apparent that his opinions

regarding the obviousness of the '122 patent were not "guided ***only*** by the prior art references and the then-accepted wisdom in the field." *Kotzab*, 217 F.3d at 1369 (emphasis added). Instead, this and other evidence adduced at trial confirms that Dr. Lenz improperly formed his opinions "with the claimed invention in mind." *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 313 (Fed. Cir. 1985). (*See also* P&G Br. at 18-20.)

B. Teva's Proposed Definition of a Person of Ordinary Skill in the Art is Unsupported by the Evidence.

In an apparent attempt to qualify its expert, Teva mounts various (and unsupported) attacks on P&G's definition of a person of ordinary skill in the art. Teva claims that (like Dr. Lenz) a person of ordinary skill in the art would not have required special training in organophosphorus chemistry because it was a "well-developed field" by 1985, and that "chemistry of the compounds was well understood." (Teva Br. at 16.) As an initial matter, Teva's argument fails because the chemistry of bisphosphonate compounds necessarily includes their properties, which, as the record demonstrates, were not "well-understood" in the mid-1980s. (*See, e.g.*, Tr. at 567:19-579:5 (McKenna Dir.); PTX 356; PTX 355; PTX 460; PTX 461).

Moreover, Teva cites ***no evidence*** from the record to support this assertion because there is none. At trial, P&G demonstrated that the art relevant to the '122 patent relates to "pharmaceutical compositions containing geminal [bis]phosphonates," (JTX 1, col. 1:1-2), "which are useful in treating or preventing diseases characterized by abnormal calcium and phosphate metabolism, in particular those which are characterized by abnormal bone metabolism." (JTX 1, col. 1:13-15). The evidence presented by P&G also shows that, given the lack of knowledge and understanding of the properties and mechanisms of action of bisphosphonates, one of ordinary skill in the art would necessarily need, as Dr. McKenna opined,

training, education and experience with organophosphorus compounds in order to understand and work with the technology relevant to the '122 patent. (P&G Br. at 13; PFF ¶ 213; Tr. at 556:1-3, 558:21–559:4 (McKenna Dir.)). *See also Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 228 F. Supp. 2d 480, 501 (D. Del. 2002) (person of ordinary skill in the art in the mid-1980s would have a "knowledge of the pharmacology and/or mechanisms of action of bisphosphonates").

Teva also makes the unsubstantiated assertion that persons skilled in the art "often had not worked with [specific] drugs before they began a new project." (Teva Br. at 16.) Again, Teva offers no evidentiary support for this assertion. Moreover, Teva's expert offered ***no opinion*** on this topic, and instead simply described his ***own*** personal experience. However, Dr. Lenz's personal experiences with drug discovery are irrelevant to determining the level of skill of one of ordinary skill in the art, particularly given that Dr. Lenz admitted that "[b]ack in the middle of the 1980s [he] did not work in bisphosphonates or phosphorus chemistry." (PFF ¶ 220; Tr. at 203:7-9 (Lenz Cross)). Because Teva has offered no support for this position *other than* the personal experience of Dr. Lenz (which did not include working in the relevant field in the mid-1980s), Teva's position lacks merit. *See* Fed. R. Evid. 702 (expert witness must have "knowledge, skill, experience, training, or education" in relevant subject area).

C. The Evidence Demonstrates that, to One of Ordinary Skill in the Art in the Mid-1980s, Bisphosphonates were Highly Unpredictable.

Despite the evidence presented at trial and the findings of this Court in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 228 F. Supp. 2d 480, 503 (D. Del. 2002), (which also involved a bisphosphonate for the treatment of osteoporosis,) Teva continues to assert that one of ordinary skill in the art could predict the structure-activity relationship of bisphosphonates in the mid-1980s. (Teva Br. at 31.) Although some credit must be given to Teva for its dogged refusal to

abandon this argument, the mountain of evidence to the contrary cannot be ignored. (*See* P&G Br. at 28-31.)

As demonstrated by P&G at trial and explained in detail in its opening brief, researchers in the mid-1980s only had an "embryonic" understanding of the relationship between bisphosphonate structure and bone activity. (P&G Br. at 29; PFF ¶ 140; Tr. at 365:14-17 (Bilezikian Dir.)). At that time, there was virtually no understanding of how bisphosphonates actually worked in treating osteoporosis, forcing researchers to speculate about possible mechanisms of action. (PFF ¶ 178; Tr. at 837:12-21 (Miller Dir.); PFF ¶ 179; Tr. at 580:16-24 (McKenna Dir.)). Consequently, the effect a particular structural change would have on the properties of any particular bisphosphonate could not be predicted in the mid-1980s.[5] (PFF ¶ 187; Tr. at 597:3-7 (McKenna Dir.)).

The unpredictability of the structure-activity relationship of bisphosphonates in the mid-1980s was recognized contemporaneously by leading researchers in the field. (P&G Br. at 29.) In 1984, Dr. Fleisch, the preeminent authority on bisphosphonates, observed that "[t]he potency of inhibiting bone resorption varies widely between different bisphosphonates and ***no relation has yet emerged between the structure of the bisphosphonate and its effect on bone resorption***." (PFF ¶ 199; Tr. at 573:12-16 (McKenna Dir.); PTX 355 at 37 (emphasis added)). He also stated that "[t]o infer from one compound the effects in another is dangerous and can be misleading." (PFF ¶198; PTX 355 at 33; Tr. at 572:9-573:1 (McKenna Dir.)). Even as of 1991, researchers such as Dr. Fleisch believed that "small changes in the structure of the bisphosphonates can lead to extensive alterations in their physicochemical, biological,

[5] Teva suggests that P&G made mere "assertions" regarding the unpredictability of bisphosphonates. (Teva Br. at 30). The evidence presented at trial demonstrates otherwise. (*See, e.g.*, PFF ¶¶ 188-210, 438; PTX 356, 355, 460, 461; Tr. at 563, 567-579, 615-616 (McKenna Dir.)).

therapeutic and toxicological characteristics" and that one "cannot necessarily extrapolate results from one compound to others." (PFF ¶ 203; PTX 460 at 921; Tr. at 576:1-12 (McKenna Dir.)). (*See also* PFF ¶ 204; Tr. at 577:11-24 (McKenna Dir.); PTX 460 at 924 ("[t]he mechanism of bisphosphonate inhibition of bone resorption [was] still not clear."). This had not changed by 1993, when Dr. Fleisch observed that the variability in properties among bisphosphonates "makes it impossible to extrapolate with certainty from data for one compound to others, so that each compound has to be considered on its own, both with respect to its use and its toxicology." (PFF ¶ 207; PTX 461 at 29; Tr. at 578:16-23 (McKenna Dir.)).

Faced with this evidence, Teva argues that the articles written by Dr. Fleisch in the mid-1980s do not demonstrate unpredictability. (Teva Br. at 30.) Other than simply saying it, however, Teva has offered ***no support*** for its assertion.[6] (*See id.*) Moreover, this argument misconstrues the issue relevant to an obviousness determination; namely, "whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success." *Life Techs., Inc. v Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000). All of the record evidence, of which the articles written by Dr. Fleisch are exemplary, demonstrate that from the perspective of a person of ordinary skill in the art in the mid-1980s (and even in the 1990s), one could not predict the activity of a bisphosphonate based on its structure alone. (P&G Br. at 28-31; PFF ¶¶ 188-210, 438.) *See also Life Techs.*, 224 F.3d at 1326 ("Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art.").

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[6] Based upon Dr. Lenz's admitted lack of experience and expertise with organophosphorus chemistry and bisphosphonates, Dr. Lenz cannot offer any reliable opinion relating to the papers authored by Dr. Fleisch. These papers are clearly directed to bisphosphonates and not to Dr. Lenz's alleged expertise in medicinal chemistry. At the very least, Dr. Lenz's interpretation of these papers, therefore, should be ignored.

Teva also claims that the properties of any particular bisphosphonate could be predicted in the mid-1980s because "virtually all" bisphosphonates exhibit some "resorption inhibition activity." (Teva Br. at 30, 45.) Again, Teva's argument misses the mark. The fact that a person of ordinary skill in the art in the mid-1980s would expect bisphosphonates to have *some* activity does not suggest that person would or could reasonably expect risedronate to have sufficient activity to be an effective treatment for metabolic bone disease and, of course, provides no information about whether the compound would be safe as a drug administered to humans. (*See* P&G Br. at 27-28.) As demonstrated at trial, the mechanism of action of bisphosphonates was unknown in the mid-1980s. (PFF ¶¶ 177-180.) Researchers therefore were unable to predict the properties of a particular compound without testing each bisphosphonate, which is the very reason P&G tested hundreds of different compounds throughout the 1980s as they searched for a next generation bisphosphonate to treat bone disease. (PFF ¶ 229.)

Given all the evidence regarding the unpredictability of bisphosphonates, (*see* PFF ¶¶ 188-210, 438), one of ordinary skill in the art in the mid-1980s would not, and in fact could not, have had a reasonable expectation of success that modifying 2-pyr EHDP to create risedronate would lead to a safe and effective treatment for metabolic bone disease. (*See* P&G Br. at 33-35.) In fact, Teva acknowledges as much in its brief. Teva admits that the mechanism of action of bisphosphonates was unknown in the mid-1980s, and, contrary to its own arguments, that tests for safety and efficacy were necessary to determine the properties of any particular compound. (Teva Br. at 5.) In other words, one could not predict the properties of a particular bisphosphonate based upon its structure alone. (P&G Br. at 29.)

V. Teva Fails to Show Invalidity of the '122 Claims Based Upon Obviousness-Type Double Patenting.

A. The Referenced Prosecution History is Irrelevant to Any Issue.

Although mentioned only by Teva once during trial (and only in its opening argument), Teva devotes a significant portion of its brief to a discussion of the pace of prosecution of the '122 patent, and in particular, the interference proceeding with U.S. Patent No. 4,687,767.[7] (*See* Teva Br. at 10-12.) In doing so, Teva appears to contend that P&G engaged in some nefarious plot to delay issuance of the '122 patent, and in particular to delay issuance of the risedronate claims. Not only is Teva wrong, but its discussion of the interference is irrelevant to any issue in this litigation.

The thrust of Teva's argument is that P&G "could have" or "should have" taken certain steps in the interference proceeding that occurred during the prosecution of the '122 patent. (Teva Br. at 11-12.) As an initial matter, Teva's unsupported speculation about what P&G "could have" done or what "should have" happened is irrelevant and inadmissible. *Invitrogen Corp. v. Clontech Labs. Inc.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005) ("Unsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony."). Moreover, Teva elicited no testimony and offered no evidence whatsoever regarding the interference. There was good reason for Teva's failure to attempt to introduce such evidence: the interference is legally irrelevant to the validity of the '122 patent,

[7] The interference was also mentioned once during P&G's opening statement. (*See* Tr. at 39:3-6) ("There was an interferences as Mr. Galbraith said. Actually, Your Honor, what happened at the patent office is not relevant to any issue that stands before Your Honor today.").

and had Teva properly raised the issue of the interference at trial, P&G would have fully rebutted Teva's erroneous assertions.[8]

B. Teva Mischaracterizes the Prosecution History.

Teva's characterization of the prosecution of the '122 patent is replete with misstatements and omissions of many critical facts. Teva, for example, neglects to mention the fact that claims encompassing risedronate and its use in pharmaceutical compositions and methods of treatment were included in the '122 patent application as initially filed in 1985 (*e.g.*, claims 21, 35, 44 and 54). (*See* JTX 2 at 37, 42, 43, 45) Teva also does not tell the Court that, even if a claim is deemed "allowable," it will not issue if it is deemed to interfere with an issued patent. *See* 37 C.F.R. §§ 1.603, 1.606; MPEP §§ 2303, 2306.01 (7th ed. 1998). Likewise, Teva does not tell the Court that P&G specifically tried to convince the Patent Office that claims encompassing risedronate should ***not*** be included in the interference. (JTX 2 at 104-05, 134-36, 159-61). The Patent Office, however, initially did not accept P&G's argument and included the risedronate claims in the interference. (JTX 4 at 2-7.)

Ultimately, upon P&G's motion, the Patent Office did remove the claims related to risedronate from the interference. (JTX 4 at 120.) However, that action did not mean that these claims could simply be "issued in a patent" as alleged by Teva. (Teva Br. at 11.) First, at the time, the Patent Office would suspend related applications during the course of an interference. *See* MPEP §2315.01 (7th ed. 1998). Second, the decision to grant P&G's motion to remove the

[8] Teva's failure to advance this argument at trial effectively waived the argument. *Cf. CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1370 (Fed. Cir. 2002) (arguments not raised at trial are waived on appeal). Moreover, had Teva attempted to make such unsupported and speculative assertions at trial, P&G would have presented the expert testimony of its interference expert, Mr. Jerry Voight, to rebut such arguments. Having lost its motion to strike Mr. Voight's testimony, Teva's failure to make these baseless arguments at trial and instead to raise them now for the first time appears to have been calculated to avoid giving P&G an opportunity to present such evidence in rebuttal. This tactic is clearly improper and should be rejected.

claims encompassing risedronate was an interlocutory ruling of a single Examiner-in-Chief ("EIC"), which under the rules of the Patent Office, could be subject to review at the conclusion of the interference. *See* 37 C.F.R. §1.640(b). Such interlocutory rulings were often reversed. *See* 37 C.F.R. §1.655(a).[9] Thus, contrary to Teva's unsupported allegations, there is no legitimate basis to suggest that P&G "could have" successfully prosecuted the risedronate claims in a separate application during the pendency of the interference. Similarly, there is no legitimate basis for assuming, as Teva does, that the risedronate claims "could have been issued" or "would probably have issued" before the Federal Circuit appeal in the interference proceeding was complete. *See Boises v. Benedict*, 27 F.3d 539 (Fed. Cir. 1994).

C. Any "Delay" Is Irrelevant Under a One-Way Test.

Teva's arguments about alleged "delay" by P&G in the prosecution of the '122 patent are of no relevance to the double patenting question before the Court. Alleged "delay" by a patentee is only relevant in deciding whether to apply a "one-way" or a "two-way" test for double patenting. *See e.g., In re Braat,* 937 F.2d 589, 593 (Fed. Cir. 1991) (two-way test applies when earlier filed application issues first and applicant had no control over rate of prosecution); *In re Emert,* 124 F.3d 1458, 1461 (Fed. Cir. 1997) (one-way test applies when earlier filed application issues first and applicant orchestrated the slower rate of prosecution). As Teva is aware, in the present case, P&G has not asserted that it is entitled to the two-way test. Thus, whether or not P&G engaged in any delay in prosecuting the risedronate claims (which it did not) is irrelevant to the double patenting analysis here.

[9] This rule was amended in 1999 to make clear that the Board will resolve the merits of an interference with no deference given for any interlocutory matters decided by a single EIC (now known as an Administrative Patent Judge).

D. Under the Appropriate Legal Standard, the '122 Patent is Not Invalid for Obviousness-Type Double Patenting.

Teva contends that the double patenting analysis differs from an obviousness determination under 35 U.S.C. § 103 in three respects:

First, as correctly noted by Teva, only the claims of the two patents are compared in an obviousness-type double patenting analysis. *See Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001).

Second, citing *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377-78 (Fed. Cir. 2003), Teva asserts that objective indicia of non-obviousness are not to be considered in obviousness-type double patenting analysis. (Teva Br. at 23, 45.) This statement of the law is erroneous. *Geneva* does not hold that objective indicia of non-obviousness *cannot* be considered in cases involving a claim of ***obviousness-type*** double patenting. Instead, *Geneva* states only that objective indicia ***may*** be ignored in a case of *anticipation-type* double patenting (which is not at issue here), and *Geneva* has been distinguished on this basis. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 911 (S.D. Ind. 2005) (obviousness-type double patenting mirrors obviousness analysis under *Graham v. John Deere Co.*, 383 U.S. 1 (1966)); Manual of Patent Examining Procedure (hereinafter "MPEP") § 804(II)(B)(1) ("The factual inquiries set forth in *Graham v. John Deere Co.* . . . that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103 are employed when making an obvious-type double patenting analysis, "including" objective indicia of nonobviousness."); *cf. In re Emert*, 124 F.3d 1458, 1462 (Fed. Cir. 1997) ("Absent some indication of unexpected properties, the [patented] combination rendered [the claimed invention] obvious [for double patenting].")

Third, Teva contends "obviousness-type double patenting does not require inquiry into a motivation to modify the prior art." (Teva Br. at 23.) Again, Teva's assertion is erroneous. *See Eli Lilly*, 364 F. Supp. 2d at 911; MPEP § 804(II)(B)(1). Moreover, Teva, in its own brief, devotes more than three full pages to arguing that one would have been motivated to modify claim 15 of the '406 patent to create risedronate. (Teva Br. at 25-28.) Those arguments also fail in view of the evidence, as set forth below.

E. Teva Fails to Properly Compare the Claims of the '122 and '406 Patents.

For obviousness-type double patenting, the claims at issue must be compared to the reference patent claim as a whole. *General Foods Corp. v. Studiengesellschaft Kohle*, 972 F.2d 1272, 1274-75 (Fed. Cir. 1992) ("patent claims, being definitions which must be read *as a whole*, do not 'claim' or cover or protect all that their words may disclose."); *Id.* at 1277-78 ("Double patenting is altogether a matter of what is claimed. . . . Claims must be read as a whole in analyzing a claim of double patenting."); *Carman Indus., Inc. v. Wahl*, 724 F.2d 932, 940 (Fed. Cir. 1983) ("we wish to clarify that double patenting is determined by analysis of the claims as a whole"). Teva, however, never makes the required comparison between the ***entirety*** of claim 15 of the '406 patent and the asserted claims of the '122 patent. (*See* Teva Br. at 17-19.)

Instead, Teva focuses on selected portions of the claim language that are helpful to it and ignores what is actually claimed in the '406 patent. In particular, Teva asserts that the "essential difference" between claim 15 of the '406 patent and the asserted claims of the '122 patent is the difference between risedronate and 2-pyr EHDP, and alleges that "[t]he inquiry, then, is whether risedronate would have been obvious in light of 2-pyr EHDP." (Teva Br. at 25.) These statements mischaracterize the substance of the '406 patent. The '406 patent does not claim the compound 2-pyr EHDP, a composition comprising 2-pyr EHDP, or a general method of using such a compound. Indeed, claim 15 of the '406 patent claims a specific dosing regimen. (JTX 5,

col. 17:33-45; col. 18:32-53.) Acknowledging as much in its brief, Teva never presents claim 15 of the '406 patent in its entirety when comparing it to the asserted claims. (*See* Teva Br. at 17-19.)

By ignoring the majority of the claim, Teva mischaracterizes the differences between the asserted claims of the '122 patent and claim 15 of the '406 patent. Based on its selective reading of the language of claim 15, Teva makes the unsupported assertion that the "essential difference between claim 15 of the '406 patent and claim 4 of the '122 patent is that the latter is specific to risedronate rather than describing the use of 2-pyr EHDP, its isomer." (Teva Br. at 25.) As described in P&G's opening brief, the differences between claim 15 of the '406 patent and claim 4 of the '122 patent are numerous. (P&G Br. at 48-49; PFF ¶¶ 417-422.) A comparison of the claims as a whole in their entirety shows just how different the claimed inventions of the two patents truly are:

Claim 15 of '406 Patent[10, 11]	**Claim 4 of '122 Patent**	**Claim 16 of '122 Patent**	**Claim 23 of '122 Patent**
1. A method for treating osteoporosis, in humans or lower animals afflicted with or at risk to osteoporosis, comprising administering to said human or lower animal an effective amount of a bone resorption inhibiting polyphosphonate ***according to the following schedule:***	4. A diphosphonic acid compound, or pharmaceutically-acceptable salt or ester thereof, which is 2-(3-pyridyl)-1-hydroxyethane diphosphonic acid.	16. A pharmaceutical composition comprising 2-(3-pyridyl)-hydroxyethane diphosphonic acid or a pharmaceutically-acceptable salt or ester thereof, at a level providing from 0.001 to 600 milligrams	23. A method of treating diseases associated with abnormal calcium and phosphate metabolism, comprising administering to a person in need of such treatment a safe and effective amount of a composition of claim 16.

[10] The bolded and italicized language represents the claim language that was omitted from Teva's representation of claim 15 in its comparison. (*See* Teva Br. at 17-19.)

[11] Claim 15 of the '406 patent and claims 16 and 23 of the '122 patent have been rewritten as independent claims to include all of their limitations.

Claim 15 of '406 Patent[10, 11]	Claim 4 of '122 Patent	Claim 16 of '122 Patent	Claim 23 of '122 Patent
(a) a period of from about 1 day to about 90 days during which said bone resorption inhibiting polyphosphonate is administered daily in a limited amount; followed by ***(b) a rest period of from about 50 days to about 120 days; and*** ***(c) repeating (a) and (b) two or more times where a net increase in bone mass said human or animal results,*** wherein the bone resorption inhibiting polyphosphonates, and daily dosage ranges, are selected from the group consisting of: ***Ethane-1-hydroxy-1,1-diphosphonic acid: from about 0.25 mg P/kg to about 4 mg P/kg;*** ***Dichloromethane diphosphonic acid: from about 0.12 mg P/kg to about 5 mg P/kg;*** ***Propane-3-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg***		phosphorus in said composition; and (b) a pharmaceutically-acceptable carrier.	

Claim 15 of '406 Patent[10, 11]	Claim 4 of '122 Patent	Claim 16 of '122 Patent	Claim 23 of '122 Patent
P/kg to about 1 mg P/kg; ***Butane-4-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;*** ***Hexane-6-amino-1-hydroxy-1,1-diphosphonic acid: from about 0.025 mg P/kg to about 1 mg P/kg;*** ***2-(2-pyridyl-ethane-1,1-diphosphonic acid: from about 0.0025 mg P/kg to about 0.1 mg P/kg;*** 2-(2-pyridyl)-1-hydroxy-ethane-1,1-diphosphonic acid: from about 0.00025 mg P/kg to about 0.01 mg P/kg; ***and/or*** ***Hexahydroindan-2,2-diphosphonic acid: from about 0.25 mg P/kg to about 10 mg P/kg;*** ***and their pharmaceutically-acceptable salts and esters.***			

By comparing the entirety of claim 15 of the '406 patent to claims 4, 16 and 23 of the '122 patent, it is apparent that the claims have fundamental differences. As demonstrated in the table above, claim 15 is a method claim for a specific "on-off" regimen for administering bisphosphonates to a patient. (PFF ¶ 392; Tr. at 871:24-872:10 (Miller Dir.)). As Dr. Lenz recognized, the "heart of the invention" of the '406 patent is a bisphosphonate dosing regimen "which does not result in a significant inhibition of bone formation." (PFF ¶ 414; Tr. at 254:12-15 (Lenz Cross); JTX 5, col. 2:18-22). This dosing regimen includes administration of a bisphosphonate for a period of from one to ninety days, followed by a rest period of about 50 to 120 days during which no bisphosphonate is administered. (PFF ¶ 392; Tr. at 608:12-18 (McKenna Dir.); JTX 5, col. 2:67–col. 3:8.) In conjunction with this dosing regimen, claim 15 lists eight different "examples" of compounds that may be used in the method, of which 2-pyr EHDP is just one. (JTX 5, col. 18:32-53.)

F. Claim 15 of the '406 Patent Does Not Render the Asserted Claims of the '122 Patent Obvious.

Teva contends that "[b]ased on claim 15 of the '406 patent a person of ordinary skill in the art would have understood 2-pyr EHDP to be safe and effective for the treatment of osteoporosis." (Teva Br. at 26.) This assertion is made without citation to the record, and there is nothing claimed in claim 15 of the '406 patent which suggests the use of 2-pyr EHDP outside of the claimed dosing regimen. (*See* JTX 5, col. 18:32-53.)

Moreover, Teva's position is contradicted by what was known in the art, as evidenced by the '406 patent itself. In 1985, one of ordinary skill in the art could not reasonably expect that 2-pyr EHDP would generally be safe and effective for the treatment of osteoporosis, as is alleged

by Teva.[12] Instead, in the mid-1980s, it was recognized that bisphosphonates could be problematic when administered because they inhibited both bone resorption and bone mineralization. (JTX 5, col. 1:60 – col. 2:7.) This was a serious problem, particularly because bisphosphonates are administered chronically for long periods of time. (JTX 5, col. 1:60-66 ("[Polyphosphonates] have, thus far, not proven to be particularly useful in diseases such as osteoporosis where there is chronic loss of bone, and therefore a perceived need for chronic treatment. The reason for this probably lies in the tight coupling between the bone resorption and formation in the human skeleton.").

In response to this problem, the '406 patent teaches one of skill in the art that the problems associated with the use of polyphosphonates in the treatment of osteoporosis (*i.e.* chronic inhibition of bone resorption with chronic inhibition of bone formation, leading to bone fractures) can be overcome ***if*** a specific dosing regimen is followed. (P&G Br. at 22-24; PFF ¶¶ 392-398; JTX 5, col. 2:8-12.) The '406 patent emphasizes that "[s]trict compliance with the above-described cyclic regimen is believed to be essential for its success" (JTX 5, col. 14, l. 29). Therefore, the '406 patent does not suggest, and in fact teaches away from modifying and using 2-pyr EHDP for the treatment of bone disease without the claimed dosing regimen. (P&G Br. at 25-26; PFF ¶¶ 171, 172; Tr. at 371:10-21 (Bilezikian Dir.); Tr. at 248:8-11 (Lenz Cross)). *See also Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000) ("teaching away" will overcome a showing of obviousness).

[12] Regarding safety, Teva asserts that "the data in the ['406] specification show that 2-pyr EHDP did not cause a statistically significant inhibition of bone mineralization at the highest dose level at which the assay was conducted. (JTX5, Table III.)" (Teva Br. at 20). However, Teva omits the fact that 2-pyr EHDP was found to be "lethally toxic at 1 mg P/kg/day." (JTX 5, col. 13:38-39).

Further, unlike claim 4 of the '122 patent, claim 15 of the '406 patent does not teach or suggest a particular compound, such as risedronate, as a compound *per se*. Nor does claim 15 teach or suggest a pharmaceutical composition comprising risedronate in the specified amount as claimed in claim 16. In fact, the '406 patent teaches a specific dosing range for 2-pyr EHDP that is narrower than the dosing range claimed for risedronate in claim 16 of the '122 patent. (*See* P&G Br. at 23; PFF ¶¶ 420-21.) It would not have been obvious to one of ordinary skill in the art, based on the dosing regimen and dosing ranges set forth in the '406 patent, that one could have administered a particular bisphosphonate on a long-term, daily basis at the much higher doses claimed in claim 16 of the '122 patent. (PFF ¶ 422.)

Finally, the method of treatment in claim 15 is vastly different from that in claim 23 of the '122 patent. Given claim 15's prescription of a specific dosing regimen, it not only fails to suggest that a general method of treatment could be used with the specified compounds, but indeed tends to teach away from such a general method of treatment. *See Winner*, 202 F.3d at 1350; *Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

Therefore, based on a reading of claim 15 as a whole, one of skill in the art would not, and could not, have understood 2-pyr EHDP, or any of the compounds disclosed therein, to be a safe and effective treatment separate and apart from the claimed dosing regimen. (P&G Br. at 15, 22-24, 28-31; PFF ¶¶ 407-08; Tr. at 633:14 – 634:24 (McKenna Dir.)). Thus, it would not have been obvious to one of ordinary skill in the art to select 2-pyr EHDP and modify that compound to make risedronate. Nor would it have been obvious to employ risedronate in a pharmaceutical composition or to administer it in a method of treatment ***without*** using the specified dosing regimen. (P&G Br. at 22-24.) Accordingly, when comparing the claims "as whole," it is apparent that the asserted claims of the '122 patent and claim 15 of the '406 patent

are patentably distinct. *See Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001).

G. Claim 15 Provides No Motivation to Modify 2-pyr EHDP.

Moreover, as explained in P&G's opening brief, there is nothing in claim 15 of the '406 patent, considered as a whole, that would lead a person skilled in the art to select the 2-pyr-EHDP compound over the numerous other bisphosphonates identified for use in the claimed dosing regimen. (P&G Br. at 47-49; PFF ¶ 407; Tr. at 614:2-6; 614:20-23 (McKenna Dir.). *Carman Indus., Inc. v. Wahl*, 724 F.2d 932, 940 (Fed. Cir. 1983); *General Foods Corp. v. Studiengesellschaft Kohle*, 972 F.2d 1272, 1274-1275 (Fed. Cir. 1992). The bisphosphonates in claim 15 of the '406 patent are of varied structure and there is no direction given regarding which structural features are preferred or particularly advantageous. (PFF ¶¶ 404-05; Tr. at 612-614:2-16 (McKenna Dir.)). In looking at the '406 patent claims, not a single claim is directed specifically to the use of 2-pyr EHDP in the claimed dosing regimen. (PFF ¶ 400; Tr. at 708:1-7 (McKenna Redir.); JTX 5, col. 17:32-col. 19:15). In contrast, there are specific claims – claims 17, 18 and 19 – that specify the use of several of the non-pyridyl, non-nitrogen containing bisphosphonates – EHDP, Cl_2MDP and HIP – in the claimed dosing regimen. (PFF ¶ 400; Tr. at 612:4-7, 706:23-708:1 (McKenna Dir.); JTX 5, col. 19-20).

Therefore, Teva has failed to identify any suggestion or motivation in claim 15 of the '406 patent to select 2-pyr EHDP over the other claimed bisphosphonates, and none exists. Teva's use of hindsight in selecting 2-pyr EHDP and completely ignoring the full breadth of what is actually claimed in claim 15 of the '406 patent is improper.

H. Teva Ignores the Significant Differences Between 2-pyr EHDP and Risedronate.

Even focusing (incorrectly) only on claim 15's disclosure of 2-pyr EHDP, Teva's obviousness arguments fail for the following reasons.

1. Risedronate is a Different Compound From 2-Pyr EHDP.

Multiple times, Teva asserts without equivocation that the "only difference" between risedronate and 2-pyr EHDP is the point of attachment of the pyridyl group and that they are "identical" except for that difference. (Teva Br. at 9-10, 18, 29.) Teva's assertions are incorrect, and ignore the testimony of Dr. McKenna that significant differences between the compounds do indeed exist. For example:

- While 2-pyr EHDP and risedronate (*i.e.*, 3-pyr EHDP) may appear similar in a 2-dimensional depiction, such a representation does not accurately represent the size, shape, and properties of a molecule. (PFF ¶ 434 (Tr. at 593:4-15 (McKenna Dir.)).
- The compounds would have differences in charge distribution, polarity and hydrogen. (PFF ¶ 435 (Tr. at 594:5-7, 594:12-595:13 (McKenna Dir.)).
- As a result of the difference in location of the nitrogen, 2-pyr EHDP and 3-pyr EHDP would have different physical, chemical, and biological properties. (PFF ¶ 435 (Tr. at 594:8-11 (McKenna Dir.)).
- The compounds "could have very profound effects at different levels of pharmacological action." (PFF ¶ 435 (Tr. at 593:20-595:20 (McKenna Dir.)).
- Due to the position of the nitrogen in the pyridyl ring, 2-pyr EHDP and risedronate will interact differently on the surface of the bone. (PFF ¶¶ 440-44; Tr. at 584:12 – 585:15 (McKenna Dir.); Slides P-22, P-24).
- Risedronate and 2-pyr EHDP interact differently with the enzyme that plays a role in the bone remodeling process. (PFF ¶¶ 446-56; Tr. at 591:21 – 592:6 (McKenna Dir.); Slides P-22, P-23).

2. Teva's Argument Shows Risedronate's Properties Are Unexpected.

If Teva were correct that risedronate and 2-pyr EHDP are "identical" except for one small change in structure, then the differences in activity demonstrated at trial would truly be

unexpected. The fact that 2-pyr EHDP killed all of the test animals at the relatively low dose of 1.0 mg P/kg/day, (Tr. at 743:14-19 (McOsker Dir.); PTX 518 at PG 191444), while risedronate showed more than a 200% increase in bone volume at that dose, (Tr. at 743:20-744:4 (McOsker Dir.); Tr. at 751:5-752:23 (McOsker Cross); Tr. at 863:4-864:9 (Miller Dir.); PTX 22 at PG 23101; P-39), would have been, and indeed was, truly surprising and unexpected. (PFF ¶¶ 335-336). The difference in efficacy between 2-pyr EHDP and risedronate in the Schenk assay based upon histological analysis likewise would have been, and in fact was, surprising and unexpected. (*See* PFF ¶ 337; Tr. at 859:19-864:9 (Miller Dir.); P-39).

Similarly, the differences in toxicity between the two allegedly "identical" compounds would have been (and in fact were) surprising and unexpected, *e.g.*, the NOEL for risedronate was determined to be 0.75 mg P/kg/day, (Tr. at 777:19–778:6 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 82 at PG 57087), while that for 2-pyr EHDP was 0.25 mg P/kg/day. (Tr. at 780:11-782:13 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 81 at PG 57031; PFF ¶ 354, 362.) The results obtained at the different toxicity data points further show unexpected differences in the properties of risedronate and 2-pyr EHDP. For example, in comparison to the renal and kidney toxicity that P&G observed for 2-pyr EHDP at the 0.75 dose, P&G saw no such toxicity for risedronate at that dose. (Tr. at 782:14-21 (Eastman Dir.); *compare* PTX 81 to PTX 82). (*See* PFF ¶ 364.)

I. The '122 Patent Claims Do Not Extend the Patent Term of Claim 15.

Despite Teva's suggestion to the contrary, public policy does not dictate that the patent term for risedronate should be shortened based upon the earlier issuance of the '406 patent. Claim 15 of the '406 patent would not be infringed by practicing the invention of claims 4, 16 and 23 of the '122 patent. Nor would claims 4, 16 and 23 be infringed by practicing the

invention of claim 15 of the '406 patent. The '122 patent thus does not extend the patent term of the '406 patent.

VI. Teva Failed to Demonstrate the '406 Patent is Prior Art Under Section 103.

A. Teva's Focus in Its Brief on Double Patenting Serves as a Concession That the '406 Patent is Not Prior Art.

In its brief, Teva focuses almost entirely on obviousness-type double patenting with very little attention to its argument of obviousness under Section 103. Teva's focus on the narrower, more stringent doctrine of obviousness-type double patenting is tantamount to a concession that the '406 patent is not prior art to the '122 patent. This concession is also apparent from the weakness of Teva's legal and factual arguments under Section 103, as set forth below.

B. Teva Must Prove That the '406 Patent is Prior Art by Clear and Convincing Evidence.

Although Teva again fails to acknowledge it, the burden of proving that the '406 patent is prior art rests upon Teva, and that burden is one of clear and convincing evidence. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1578 (Fed. Cir. 1996); *Innovative Scuba Concepts, Inc. v. Feder Indus., Inc.*, 26 F.3d 1112, 1115 (Fed. Cir. 1994). Where a defendant challenges a patent on obviousness grounds with a reference document published before the filing date of the patent at issue, the patent holder merely needs to meet a burden of production by coming forward with evidence showing he invented the subject matter of his patent before the publication date of the reference document. *Mahurkar*, 79 F.3d at 1576-77. Once this burden of production is met, the Court turns to an evaluation of the evidence offered by the defendant challenging the patent under the proper burden of persuasion of clear and convincing evidence on all issues relating to the status of the reference document as prior art. *Id.* at 1576; *Innovative Scuba*, Inc., 26 F.3d at 1115 (Fed. Cir. 1994). As discussed below, Teva has failed to meet this burden.

C. Dr. Benedict's Trial Testimony and Lab Notebook Entries Demonstrate Conception of Risedronate on May 3, 1985 Prior to the '406 Patent.

In attempting to attack the priority of the '122 patent over the '406 patent for purposes of its Section 103 obviousness analysis, Teva incorrectly states that an inventor's unwitnessed lab notebook is insufficient to corroborate conception and that the unwitnessed notebooks "can not [sic] as a matter of law be relied upon to corroborate Dr. Benedict's oral testimony of conception." (Teva Br. at 50-51.)[13] This legal proposition is incorrect. In fact, courts apply a "rule of reason" analysis to determine whether an inventor's prior conception testimony is corroborated, evaluating all pertinent evidence "so that a sound determination of the credibility of the inventor's story may be reached." *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993).[14] While oral testimony of an inventor standing alone requires corroboration, physical evidence provided in support of oral testimony does not require corroboration because "the trier of fact can conclude for itself what the documents show." *Brown v. Barbacid*, 276 F.3d 1327, 1335 (Fed. Cir. 2002) (quoting *Mahurkar*, 79 F.3d at 1577-78). Under this rule of reason analysis, signed lab notebooks, even if not independently confirmed (countersigned), are admissible as corroborative evidence of an inventor's oral testimony. *See Medichem, S.A. v.*

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[13] In support of its assertion, Teva cites *In re Hahn*, 892 F.2d 1028, 1032-33 (Fed. Cir. 1989). *Hahn* only holds that actual reduction to practice – an entirely different concept – cannot be corroborated wholly by an inventor's own lab notebook. *Id.* Therefore, it does not apply here.

[14] In the rule of reason analysis for corroboration, courts consider: "(1) the relationship between the corroborating witness and the alleged prior use, (2) the time period between the event and trial, (3) the interest of the corroborating witness in the subject matter in suit, (4) contradiction or impeachment of the witness' testimony, (5) the extent and details of the corroborating testimony, (6) the witness' familiarity with the subject matter of the patented invention and the prior use, (7) probability that a prior use could occur considering the state of the art at the time, (8) impact of the invention on the industry, and the commercial value of its practice." *Woodland Trust v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1371 (Fed. Cir. 1998) (citing *Price*, 988 F.2d at 1195 n.3).

Rolabo, S.L., 437 F.3d 1157, 1169-70 (Fed. Cir. 2006); *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577-78 (Fed. Cir. 1996).

Therefore, under the correct legal standard, Dr. Benedict's trial testimony of conception of risedronate is more than adequately corroborated by his signed, dated lab notebook entry of the synthesis of risedronate on May 3, 1985. (PFF ¶ 274; Tr. at 420:19-421:1, 467:5-22 (Benedict Dir.); PTX 67 at PG 53521-53522.) Moreover, the other evidence offered by P&G, such as the uncontroverted evidence that risedronate was sent for testing prior to the filing of the '406 patent application, (*see* PFF ¶ 277,) strongly supports the conclusion that Dr. Benedict conceived of risedronate prior to the filing of the '406 patent on June 6, 1985. Significantly, Teva makes absolutely no attempt to rebut this evidence other than to insinuate, without support, that Dr. Benedict's lab notebook entries might not be authentic.

D. Witness Testimony and Supporting Documents Demonstrate Diligence in Reduction to Practice.

Teva also ignores that it has the burden of proving that P&G was not diligent in reducing the invention of the '122 patent to practice either actually or constructively. In light of the statutory presumption of patent validity under 35 U.S.C. § 282, where a patented invention is conceived prior to the filing date of a reference asserted as prior art, but reduced to practice after the filing date of that reference, the party challenging the validity of a patent must prove by clear and convincing evidence that the reference patent was filed before the effective invention date for the challenged patent. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1578 (Fed. Cir. 1996); *see also Loral Fairchild Corp. v. Matsushita Elec. Indus. Co.*, 266 F.3d 1358, 1361 (Fed. Cir. 2001). That is, the challenger of the patent's validity has the burden to prove that the inventor did not proceed with reasonable diligence from a time just before the filing of the reference patent until

the challenged invention had been reduced to practice (actually or constructively with the filing of the patent). *Mahurkar*, 79 F.3d at 1578.

Notwithstanding its burden of proof, Teva offers absolutely no evidence to overcome P&G's evidence of diligence or reduction to practice and again relies instead on unfounded insinuations concerning the authenticity of P&G's documentary evidence, even in the face of witness testimony and supporting documentary evidence kept in the ordinary course of business. The testimony of Drs. Benedict and Eastman and Ms. McOsker, as well as the documents supporting their testimony, all demonstrate the requisite diligence toward reduction to practice. (*See* PFF ¶¶ 276-84, 308-26, 353-58.)

For all the reasons set forth above, Teva cannot meet its burden of proving that the '406 patent is prior art to the '122 patent.

VII. Teva Failed to Demonstrate That the '122 Patent is Obvious Under Section 103.

Even assuming, contrary to all the evidence, that the '406 patent is prior art to the '122 patent, Teva has nonetheless failed to demonstrate by clear and convincing evidence that the '122 patent is obvious in light of the '406 patent under Section 103. At most, Teva suggests that it would have been obvious ***to try*** risedronate, which is legally insufficient to meet its burden. A suggestion that an invention would have been "'obvious to try' does not equate with obviousness for purposes of Section 103." *Pfizer Inc. v. Ranbaxy Labs. Ltd*, 405 F. Supp. 2d 495, 517 (D. Del. 2005); *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) ("[T]his court and its predecessors have repeatedly emphasized that 'obvious to try' is not the standard under § 103."); *N.V. Akzo v. E.I. DuPont de Nemours*, 810 F.2d 1148, 1151 (Fed. Cir. 1987) ("Of course, an 'obvious to try' standard is not a legitimate test of patentability.").

To prove that a modified chemical structure would be obvious, there must be a reasonable expectation of success for the modified compound. Although Teva acknowledges

this, it improperly defines reasonable expectation of success as "a reasonable expectation that the resulting compound would have activity useful in treating diseases involving calcium and phosphate metabolism." (Teva Br. at 26.) This ignores toxicity altogether as well as relative potency in defining success. Teva states, "a person skilled in the art who was aware of the activity of 2-pyr EHDP would have reasonably expected risedronate likewise to have bone resorption inhibition activity." (Teva Br. at 30.) However, merely having ***some*** amount of bone resorption activity is not the test for success, as this property alone would not solve the problem the invention of the '122 patent seeks to address – finding potent bisphosphonates that exhibit less inhibition of bone mineralization for safe, pharmaceutical use in treating metabolic bone disorders.

Thus, to invalidate the asserted claims of the '122 patent, Teva was required to show by clear and convincing evidence that one of ordinary skill in the art would have had a reasonable expectation, in light of the '406 patent, that risedronate would be successful as a "more biologically potent [bis]phosphonate compound[] that can be administered at low dosage levels which cause little or no mineralization inhibition, thereby resulting in a wider margin of safety." (JTX 1, col. 2:11-18). Teva presented no such evidence. To the contrary, the record shows that in the mid-1980s, a person of ordinary skill in the art would have had ***no*** expectation, let alone a reasonable one, that any particular bisphosphonate would be both safe and effective as a treatment for bone disease. (P&G Br. 28-35.) As demonstrated at trial, and as Teva admits in its brief (*see* Teva Br. at 5), the mechanism of action of bisphosphonates was unknown, and researchers were unable to predict anything without testing each bisphosphonate, which is the very reason P&G tested hundreds of different compounds as it searched for a next generation bisphosphonate. (P&G Br. 28-31.)

For these reasons, and the reasons articulated in P&G's opening brief, (*see* P&G Br. at 10-33), Teva's principal Section 103 obviousness argument fails. In addition, as discussed below, over Teva's weak opposing arguments, the nonobviousness of the inventions of the '122 patent is further supported by strong objective indicia.

VIII. The Nonobviousness of the Inventions of the '122 Patent is Supported by Strong Secondary Considerations.

Under both a Section 103 and obviousness-type double patenting analysis, secondary considerations of nonobviousness should be fully considered. *See supra* at Section V.D. Teva does not dispute the long-felt need for a safe drug with high antiresorptive potency but low antimineralization properties, or that risedronate met that need. As discussed below, Teva's attacks on risedronate's unexpected properties and commercial success are unfounded.

A. The Record Evidence Unequivocally Demonstrates Unexpected Results.

Teva misstates the law with respect to unexpected results, suggesting that a "difference in kind" rather than a "difference in degree" must be proven. (Teva Br. at 32-33.). The Federal Circuit, however, has stated:

> [O]ur cases make clear that there is no hard-and-fast rule for determining whether evidence of unexpected results is sufficient to rebut . . . obviousness. We have stated, for example, that rebuttal of [obviousness] 'can consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties,' but also that 'each situation must be considered on its own facts.' Certainly we have stated on several occasions that unexpected results may be sufficient to rebut . . . obviousness."

Kao Corp. v. Unilever United States, Inc., 441 F.3d 963, 970 (Fed. Cir. 2006) (internal citations omitted).

Chemical homologues of prior art compounds are not obvious if they possess unexpected properties. *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995); *In re Chupp*, 816 F.2d 643, 646-47 (Fed. Cir. 1987). Evidence of unexpected results could "consist of a comparison of test data

showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990). "[W]hen an applicant demonstrates substantially improved results . . . and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." *Soni*, 54 F.3d at 751. To cite a case on which Teva relied, there are "substantial, actual differences in properties" between 2-pyr EHDP and risedronate. *See In re Hoch*, 428 F.2d 1341, 1344 (C.C.P.A. 1970).

The substantially superior testing results achieved with risedronate compared to the hundreds of other of bisphosphonates tested by P&G were unexpected and could not have been anticipated. (PFF ¶¶ 314, 316, 342, 343, 380, 383; Tr. at 476:8-18, 479:4-19, 481:19-482:10 (Benedict Dir.); 726:11-21, 727:12-17 (McOsker Dir.); 870:4-871:9 (Miller Dir.); PTX 44). Risedronate was found to be appreciably more potent as an antiresorptive agent than any other compound P&G studied, (PFF ¶¶ 342, 377; Tr. at 476:8-18, 481:19-482:10 (Benedict Dir.); PTX 148; P-036b), and to have a very favorable toxicity profile. (PFF ¶¶ 354, 359; Tr. at 476:21-477:11 (Benedict Dir.), 777:19–778:6 (Eastman Dir.); Tr. at 865:6-866:14 (Miller Dir.); PTX 82 at PG 57087.) In addition, risedronate did not inhibit bone mineralization when dosed within the therapeutic range. (*See* PFF ¶ 485.) Risedronate therefore showed an unexpected safety to efficacy ratio (or therapeutic index) in P&G's compound-screening program that was at least ***ten times*** better than any other compound tested. (Tr. at 867:10-868:20 (Miller Dir.); P-40; PTX 148 at PG 78507; P-36b.)

In particular, risedronate was found to possess unexpected results when compared to the structurally similar positional isomer, 2-pyr EHDP. As discussed *infra*, the antiresorptive activity of risedronate was more than three times that of 2-pyr EHDP, and the toxicity profile of

risedronate was three times superior to that of 2-pyr EHDP. (PFF ¶¶ 337, 339, 342; Tr. at 476:8-18, 481:19-482:10 (Benedict Dir.), 859:11-864:9 (Miller Dir.); P-39). These results and the underlying properties of the compound that give rise to them could not have been predicted or anticipated either based on the 2-pyr EHDP compound or any other compound, and were thus completely unexpected.

The requisite nexus exists between these unexpected results and the asserted claims, which are specifically directed to risedronate and its use in a pharmaceutical composition and method of treatment, and the unexpected results are based upon risedronate's inherent properties. Such unexpected properties of risedronate cannot be ignored in judging the validity of the asserted claims. *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Ortho., Inc.*, 976 F.2d 1559, 1573 (Fed. Cir. 1992) ("unexpected results must be considered before a conclusion on obviousness is reached."); *In re Lunsford*, 327 F.2d 526, 528 (C.C.P.A. 1964) (finding an "unobvious property inherent in the claimed compounds" sufficient to overcome a showing of very close structural obviousness); *In re Ward*, 329 F.2d 1021, 1023 (C.C.P.A. 1964).

1. Teva Misstates the Evidence concerning the Relative Potency of Risedronate vs. 2-pyr EHDP.

Teva attempts to challenge the superiority of risedronate's potency over that of 2-pyr EHDP by relying upon an erroneous graph containing data that was not normalized and adjusted for control. Contrary to Teva's allegations, Dr. Miller provided a thorough explanation of the error at trial and presented a properly revised version of the graph that shows the meaningful comparison of the compounds' relative antiresorptive potencies, revealing that risedronate is far more potent. (Tr. at 859:11-860:13 (Miller Dir.); Tr. at 875:14-877:15, 878:7-881:19 (Miller Cross); Tr. 937:1-938:17 (Miller Redirect); P-39.)

It is bedrock principle of the scientific method that experimental test groups be compared against a control group so that any meaningful difference between the "normal" group of subjects and the test group of subjects may be discerned, quantified, and statistically analyzed. (Tr. at 859:11-860:13 (Miller Dir.); Tr. 937:1-16 (Miller Redirect)). Here, P&G conducted experiments with two test substances – 2-pyr EHDP and risedronate – at various dose levels in separate runs of the same controlled study protocol. The graph on which Teva relies, although admittedly a graph that P&G scientists created, plots changes in trabecular bone volume[15] at various dose levels for the two runs of the Schenk protocol for 2-pyr EHDP and risedronate. As Dr. Miller explained, this comparison is meaningless in that it does not plot the changes in trabecular bone volume as percentage changes from control and instead plots absolute values for the test compounds taken out of context, because it fails to take into account differences in the control group results. (*Id.*)

As Dr. Miller explained at trial, when the data in the 2-pyr EHDP and risedronate Schenk studies are properly normalized and adjusted for their respective controls as a percentage change in trabecular bone volume from control, a significantly larger difference in potency is demonstrated as properly graphed in P-39. (Tr. at 859:11-864:23 (Miller Dir.); P-39.)[16]

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[15] Trabecular bone volume is measured as "%TBV." It is a measure of the trabecular bone per unit space or a percentage of space measured that is composed of bone versus non-bone. If, for example, one-quarter of the unit of space measured were bone, the "%TBV" would be 25.

[16] The publication of the data from the graph contained in DTX 144 at PG 67112 in tabular form that Teva references (*see* DTX 74 at 10) only confirms that Dr. Miller's methodology is the correct methodology to use in making a comparison of the data from the two Schenk studies. In the published version of the data in tabular form, the data is labeled "%TBV, expressed as % change from control," suggesting that the data reflect a percentage change from control. (DTX 74 at 10.) The published article, however, mistakenly contained the absolute changes from control rather than the percentage changes from control. The label on the graph indicates what data *should* have been presented. The data presented by Dr. Miller at trial represent what should have been published – the "% change from control" of "%TBV." (This

Teva also alleges that the 0.01 mg P/kg data point for the risedronate potency graph is biased because of a dosing excess on one day for which 1.0 mg P/kg instead of 0.01 mg P/kg was used. (Teva Br. at 39.) As Dr. Miller explained at trial, this small error in administration would not ruin the data for the 0.01 mg P/kg data point since the correct 0.01 mg P/kg dose was used for six of the seven days of dosing in the experiment at this level and would only affect a small segment of bone. (Tr. at 898:8 – 899:13 (Miller Dir.)).[17]

Teva also relies on a much later *in vitro* study in an attempt to challenge risedronate's clear potency advantage over 2-pyr EHDP. Such an *in vitro* study is inherently much less reliable than the *in vivo* studies P&G carefully conducted in studying relative potency of the compounds in its development program. As Dr. Miller testified, such studies are "notoriously well known for not predicting what occurs in the animal." (Tr. at 926:3-11 (Miller Cross)).

Finally, Teva's suggestion that the potency of risedronate "cannot" be distinguished from 2-pyr EHDP at the 0.000125 level, which Teva alleges corresponds to the equivalent human dose (*see* Teva Br. at 39), is completely baseless and lacks any foundation whatsoever. As an initial matter, the clinical dose of risedronate for human beings was not known, nor could it have been known, in 1985. Moreover, P&G was testing for relative potency overall, and its observations suggested that risedronate – at any dose – was a much more potent resorption-inhibiting compound than 2-pyr EHDP.

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measure is a percentage change from control of a metric that itself is measured as a percentage as described in footnote 15, *supra*.)

[17] Dr. Miller explained that any dosing bias would be limited to that one day's bone growth. Since trabecular bone volume is measured by taking a thin cross-section of bone from the test subject, to bias the results, the cross sections used to measure the trabecular bone volume for the 0.01 mg P/kg test group would have had to have been taken from the small section of bone in the rats corresponding to the day of the overdose (day 5 of 7). The data strongly suggests that the 0.01 mg P/kg data point was not taken from this biased section since the level of change in trabecular bone volume that was achieved did not compare to the 1.0 mg P/kg for risedronate, which was also tested and plotted on the graph. (*See* P-39.)

The attempted comparison of the compounds at this alleged "human" dose is also totally irrelevant to the determination of unexpected results. Teva seeks to manufacture a new standard for unexpected results that is convenient for its argument. The law does not require P&G to show unexpected differences in properties at a specific dose level appropriate for clinical use in human beings. Rather, to rebut obviousness, a patent holder may show an unexpected difference in properties between the patented compound and its homologue, which P&G has demonstrated. Though there is absolutely no evidence to suggest that this difference in results would be any different at the alleged human dose level (considered in hindsight), whether the unexpected difference translates to human doses is irrelevant to the legal standard.

In short, lacking any meaningful evidence to contest P&G's assertion that risedronate was surprisingly more potent than prior art compounds, including 2-pyr EHDP, Teva resorts to speculative and irrelevant assertions about what might have been. These assertions are insufficient to raise any serious question about risedronate's unexpected efficacy properties.

2. Teva's Attacks on P&G's Toxicity Data Fail.

Similarly, in the face of detailed and overwhelming evidence to the contrary, Teva attempts to pick at P&G's conclusion that risedronate had a much better toxicity profile than 2-pyr EHDP. Teva first tries to suggest, contrary to fact, that there was not a significant difference in toxicity between risedronate and 2-pyr EHDP as revealed by P&G's toxicity testing. Teva argues that having tested for toxicity at doses of 0.25, 0.75, and 2.5 mg P/kg and finding risedronate to be safe at 0.75 mg P/kg and 2-pyr EHDP to be safe at 0.25 mg P/kg, P&G cannot conclude that risedronate is three times safer than 2-pyr EHDP. Teva suggests that because intermediate doses were not tested that 2-pyr EHDP could have a much higher non-toxic level approaching 0.75 mg P/kg, which Teva alleges would make it similar in toxicity to risedronate.

This argument fails for two reasons. First, it is equally plausible that risedronate has a much higher non-toxic level approaching ***2.5*** mg P/kg. By Teva's reasoning, risedronate could actually be almost ***ten times*** safer than 2-pyr EHDP. Second, the toxicity reports for risedronate and 2-pyr EHDP reveal that the pathologies for 2-pyr EHDP were significantly more severe at the 0.75 mg dose than those for risedronate even at the higher 2.5 dose. (*See* PTX 81; PTX 82; P-36a.) This suggests that "actual" non-toxic thresholds for the two compounds are, if anything, even greater than three times in magnitude.

Teva also attempts to argue, contrary to the evidence, that 2-pyr EHDP actually showed a lower liver toxicity than risedronate. This argument is misplaced. P&G was particularly attentive to liver toxicity in its two-day, *in vivo* toxicity screen both anatomically (autopsy) and serologically (in-life blood work). The test in DTX 94 that Teva points to, in contrast, is an *in vitro* study that took place in a test tube. As stated by Dr. Miller at trial, *in vitro* studies are notoriously unreliable and less meaningful than *in vivo* studies, such as the ones P&G conducted, particularly for purposes of studying potential toxicity. (Tr. at 926:3-11 (Miller Cross)).

Lastly, Teva's calculation of "therapeutic ratio" of 2-pyr EHDP (13,000) (*see* Teva Br. at 43) lacks any foundation. It seems to be premised on using 1.0 mg P/kg as the upper margin for the calculation, which is absolutely improper. The 2-pyr EHDP compound was found to be ***lethally toxic*** at this dose because it killed every rat tested at that dose. (Tr. at 750:18-751:9 (Benedict Cross.); Tr. at 864:1-9 (Miller Dir.).) That testing, however, did not indicate that 1.0 mg P/kg was the *lowest* lethally toxic dose. Rather, that testing only revealed that 2-pyr EHDP was lethally toxic at every dose greater than 0.1 mg P/kg examined in the study. The actual dose at which 2-pyr EHDP becomes lethal could be anywhere between 0.1 mg P/kg and 1.0 mg P/kg. Indeed, P&G subsequently found 2-pyr EHDP to be toxic at 0.75 mg P/kg but safe at 0.25 mg

P/kg. (Tr. at 780:11-782:13 (Eastman Dir.); PTX 82.) The upper boundary of the therapeutic ratio calculation should be the NOEL (Tr. at 851:2-852:14 (Miller Dir.)), which for 2-pyr EHDP was found by P&G to be 0.25 mg P/kg, ***not*** 1.0 mg P/kg (Tr. at 781:18-21 (Eastman Dir.); PTX 81). Furthermore, the lower bound of therapeutic ratio is the lowest effective dose (LED) (Tr. at 851:2-852:14 (Miller Dir.)), and there is absolutely no basis on the record or otherwise to assume that 2-pyr EHDP would be an effective antiresorptive compound at the dose Teva uses in its calculation.[18]

3. Risedronate's Safety-to-Efficacy Ratio Was Ten Times Superior to Other Known Compounds.

Finally, Teva attempts to dispute P&G's showing that risedronate had a therapeutic index that was ten times better than 2-pyr EHDP. (Teva Br. at 45.) There are at least three flaws in this argument. First, although 2-pyr EHDP was not specifically tested at 0.0003 mg P/kg, the potency curves (*see* P-39) suggest that risedronate was much more effective at all doses and that 2-pyr EHDP was not likely to be effective at 0.0003 mg P/kg. Second, the separation in toxicity, which was measured as three-fold, was likely to be even larger (as discussed *supra*). Furthermore, all of Teva's assertions reflect impermissible hindsight. At the time P&G conducted the studies in question, its goal was to find the safest and most effective compound to develop for the treatment of osteoporosis. If there were any reason to believe that 2-pyr EHDP was that compound, P&G would have advanced 2-pyr EHDP (which was also within the scope of the '122 patent application) for further study. The fact of the matter, however, is that in 1985,

[18] Teva's attempted comparison between 2-pyr EHDP and alendronate (*see* Teva Br. at 43-44) is both inapt and irrelevant given the differences in structure between these compounds and the recognized inability to draw inferences from compound to another. (*See* PFF ¶ 198.) Again, Teva uses 1.0 mg P/kg dose as the upper boundary for the therapeutic window when, in fact, 2-pyr EHDP's NOEL (or highest non-toxic dose) was shown to be *much* lower than that (0.25 mg P/kg). (Tr. at 851:2-852:14 (Miller Dir.)). Whether 2-pyr EHDP compares to alendronate is also wholly irrelevant to whether 2-pyr EHDP showed a comparable safety-to-efficacy ratio to risedronate.

P&G legitimately believed, based on the results of its testing, that risedronate was the best compound by a ten-fold margin over any other compound under study. And today, there is no reason to question those findings. In fact, these findings of unexpected differences in properties are now validated by recent research on the mechanisms of action of bisphosphonates. (PFF ¶¶ 440-44, 446-56; Tr. at 584:12 – 585:15, Tr. at 591:21 – 592:6 (McKenna Dir.); Slides P-22 – P-24).

B. Actonel's Resounding Commercial Success Appropriately Supports Nonobviousness.

At trial, P&G demonstrated that (1) Actonel is a resounding commercial success, and (2) that its success is attributable to the '122 patent. (P&G Br. at 43-44.) Teva offered nothing to rebut this evidence. (*Id.* at 44-45.) Instead, through the testimony of its ostensible "rebuttal" expert, Dr. Jesse David, and now in its brief, Teva asserts that the commercial success of Actonel is irrelevant to nonobviousness because "the prior art compound [*i.e*, 2-pyr EHDP] was unknown to those in the art." (Teva Br. at 47.) Even apart from the inadmissibility of Dr. David's testimony, (*see* P&G Br. at 44-45), Teva's argument fails for two reasons.

First, Teva's argument is fundamentally flawed and internally inconsistent with its obviousness attacks on the '122 patent because, according to its arguments, 2-pyr EHDP was prior art at the time 3-pyr EHDP was invented. (*See* Teva Br. at 46-47.) Prior art is technology already available to the public. *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed. Cir. 1984).[19] For purposes of analyzing obviousness, the alleged prior art must be

[19] *See also W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983) ("Early public disclosure is a linchpin of the patent system. As between a prior inventor [who does not disclose] and a later inventor who promptly files a patent application... the law favors the latter."). *See* Section-by-Section Analysis: Patent Law Amendments Act of 1984, 130 Cong. Rec. 28069, 28071 (Oct. 1, 1984) (stating that the amendment, which encourages communication among members of research teams, was a "response to [prior holdings], in which 'an earlier invention which is not public may be treated . . . as prior art'").

disseminated, or otherwise made available, to the extent that persons interested in, and of ordinary skill in the subject matter or art, exercising reasonable diligence, can locate it. *Massachusetts Institute of Technology v. AB Fortia*, 774 F.2d 1104, 1109 (Fed. Cir. 1985). Non-public technology maintained within an organization before the patented invention is created is not prior art. *See e.g.*, *OddzOn Prods, Inc. v. Just Toys Inc.*, 122 F.3d 1396, 1403 (Fed. Cir. 1997) ("It is historically very clear that this provision [Section 103(c)] was intended to avoid the invalidation of patents under § 103 on the basis of the work of fellow employees engaged in team research."); *Continental Oil Co. v. Cole*, 634 F.2d 188 (5th Cir. 1981) (holding that intracompany memoranda are not sufficiently public to be citable as prior art).

Given the law, either 2-pyr EHDP is prior art (as Teva contends for its section 103 obviousness argument), and therefore public, or the compound was non-public at the time risedronate was invented (as Teva assumes for its argument against commercial success), and therefore is not prior art. Teva cannot have it both ways. Having taken the position that 2-pyr EHDP ***is prior art*** for purposes of its attack against the relevance of the undisputed commercial success of Actonel, (*see* Teva Br. at 47), Teva's argument must fail.

Second, Teva's reliance on and attempt to expand the Federal Circuit's decision in *Merck & Co. Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005), is insupportable. (*See* Teva Br. at 45-47.) In *Merck*, the patentee had in place two mechanisms for restricting market entry by competitors to test the suggestions of the prior art: (1) a prior patent that covered the administration of alendronate to treat osteoporosis in general; and (2) "an exclusive statutory right,[20] in conjunction with FDA marketing approvals, to offer Fosamax *at any dosage* for the

[20] When a new chemical entity receives FDA approval for the first time the submitter is granted five years of market exclusivity, in which time no generic competitor can receive FDA approval. 21 CFR § 314.108.

next five years." *Merck*, 395 F.3d at 1377 (emphasis added). The Federal Circuit held that, "[b]ecause market entry [of competitors to test the prior art suggestion of Fosamax once-weekly dose] was precluded on those bases, the inference of non-obviousness of weekly dosing from evidence of commercial success, is weak." *Id.*

The factually specific holding of *Merck* is inapplicable here. Unlike in *Merck*, P&G did not have a legal bar that would have excluded others from testing any prior art suggestion of risedronate before its invention. P&G did not hold exclusive statutory rights to risedronate until the issuance of the '122 patent in 1996. Furthermore, unlike in *Merck*, the '406 patent, which issued in 1988, did not bar others from developing risedronate or the use of risedronate outside of the specific dosing regimen claimed by the '406 patent. (*See* JTX 5.) Accordingly, Teva reads *Merck* far too broadly. *See e.g.*, *Takeda Chem. Indus., Ltd. v. Mylan Laboratories*, 417 F.Supp.2d 341, 387 n.77 (S.D.N.Y. 2006) (defendant "reads [*Merck*] far too broadly...[t]he case does not establish that commercial success is not probative simply because a patent holder also holds a prior art patent"). Therefore, the unrebutted evidence of Actonel's resounding commercial success is relevant to the nonobviousness of the asserted claims of the '122 patent.

IX. Conclusion

For the foregoing reasons, and the reasons set forth in P&G's opening post-trial brief, P&G requests that this Court find in favor of P&G, find the '122 patent valid and infringed by Teva, and grant any further relief requested in P&G's opening post-trial brief.

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Dated: January 26, 2007

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

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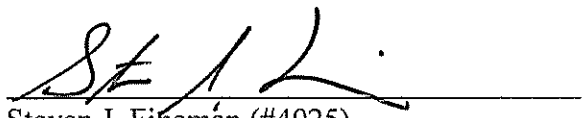

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